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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,741	12/10/2003	Thomas M. Schmitt	2223-171	5362

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EXAMINER	
LIETO, LOUIS D	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/731,741	SCHMITT ET AL.	
	Examiner	Art Unit	
	Louis D Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *18-21,23 and 25-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17, 22, and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the Restriction was received on 12/20/2004. Claims 1-28 are pending in the instant application. Applicants elected the subject matter of group I, drawn to a method of forming cells of the T cell lineage. Claims 18-21, 23, and 25-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 1-17, 22 and 24 are currently under examination. Claim 22 was rejoined by the examiner in the interests of compact prosecution. Please note that claim 24 was only examined to the extent which it reads on the subject matter of group I. Claim 24 was not examined to the extent that it reads on a composition, since this comprises unelected subject matter. It is noted that applicant did not specifically elect without traverse. However since applicant failed to argue the restriction requirement the election is being treated as if it was made without traverses. The requirement is deemed proper and is therefore made FINAL.

An action on the merits follows.

Priority

Applicant's claim of priority to US Provisional patent application No: 60/432,525 filed on December 10,2002 is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17, 22 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* system comprising OP9 stromal cells that express Delta-like 1 ligand, that supports αβ CD4+ CD8+ T cells, αβ CD4- CD8+ T cells and γδ T cell lymphopoiesis from hematopoietic progenitor cells, hematopoietic stems cells and mouse embryonic stem cells, but does not support B cell lymphopoiesis, does not reasonably provide enablement for an *in vitro* system comprising any stromal cells expressing any Notch ligand that supports any and all T cell lymphopoiesis from any cell but does not support B cell lymphopoiesis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Please note that claim 24 was only examined to the extent which it reads on the subject matter of group I. Claim 24 was not examined to the extent that it reads on a composition, since this comprises unelected subject matter. If Claim 24 is amended to read on a composition, further restriction will be required.

The specification only provides guidance on the use of OP9 stromal cells to produce αβ CD4+ CD8+ T cells, αβ CD4- CD8+ T cells and γδ T cells. The working examples only describe the use of OP9 stromal cells. Stromal cells differ in their expression of surface ligands and receptors, and therefore have different microenvironments that affect T cell lineage development. Schmitt et al. teaches that the stromal cell microenvironment for efficient *in vitro* T cell development is important; for example, while delta-like 1 expressing S17 stromal cells were able to produce immature T cell lineages, they were not able to produce mature differentiated T cell lineages {Schmitt et al. (2002) Immunity 17:749-756; pg. 754, col. 1-col.2}. Thus, since the specification does not teach the use of any other stromal cells for use in the *in vitro* system, or

the conditions necessary to duplicate the OP9 stromal cell microenvironment, the skilled practitioner would be unable to predict that use of any stromal cell in the *in vitro* system would produce αβ CD4+ CD8+ T cells, αβ CD4- CD8+ T cells and γδ T cells.

The specification only provides guidance on the use of Delta-like 1 ligands expressed by OP9 cells to produce αβ CD4+ CD8+ T cells, αβ CD4- CD8+ T cells and γδ T cells. The specification contemplates the use of Jagged 1, Jagged 2, Delta-like 1, Delta-like 3, and Delta-like 4, however the working examples only describe that OP9 expressed Delta-like 1supports T cell lymphopoiesis. Lehar et al. teaches that Jagged1 or Delta1 expression on OP9 stromal cells transmit distinct signals to T cell precursors {Lehar et al. (2004) Blood. Epub ahead of print, DOI 10.1182/blood-2004-08-3257: 1-38; Abstract}. Lehar et al states that of the two ligands, only Delta-1 expressing stromal cells promote the proliferation and maturation of T cell progenitors (Abstract; pg. 14). Similarly, Jaleco et al. reported that Delta-1 but not Jagged-1, permits the development of T cell but not B cell lineages {Jaleco et al. (2001) J. Exp. Med. 194:991-1001; Abstract; pg. 995, Table 1; pg. 996, Figure 2}. Therefore based on the teachings in the art, the skilled practitioner would be unable to predict that the invention could be successfully practiced using a cell preparation expressing any notch ligand other than Delta-like 1.

The specification does not provide enablement for the development of all T cell lineages. The working examples do not demonstrate that all mature T cell subset, specifically αβ CD4+CD8- T cells, can be developed using this *in vitro* system. Rothenberg teaches that culturing precursors with OP9 cells that express Delta-like 1 only enables the generation of αβ CD4+CD8+ T cells, and mature αβ CD4-CD8+ T cells and γδ T cells {Rothenberg (2004)

Nature Immunology 5:359-360; col.1, pgph 1}. Finally, Schmitt et al. were unable to demonstrate the production of mature CD4+CD8- T cells using an *in vitro* system comprising OP9 stromal cells that express Delta-like 1 {Schmitt et al. (2004) Nature Immunology 5:410-417; pg. 415, col.1 pgph 3}. Rothenberg states that the OP9-DL1 system is limited because it does not allow positive selection of αβ CD4+ CD8- T cells inability, due to the lack of MHC II expression (pg. 360, col.2, pgph 1). Thus, the skilled practitioner would be unable to produce αβ CD4+CD8- T cells using the *in vitro* system as claimed.

The specification does not teach that T cells can be developed from any and all cells. The working examples do not describe that terminally differentiated cells such as fibroblasts, melanocytes or epithelial cells can be induced to form T cells, at any stage. Further, the specification does not teach that any species of embryonic stem cells (ESCs) can be used in the *in vitro* system to form T cells. The phrase ESCs has a distinct meaning in the art. Thomson et al. teaches that the defining characteristics of the ES cell is, (i) derivation from the preimplantation or periimplantation embryo, (ii) prolonged undifferentiated proliferation, and (iii) stable development potential to form derivatives of all three embryonic germ layers {Thomson et al. (1998) Science, Vol. 282, page 1145, paragraph 1}. John Gearhart, in a review of Thomson et al. article, explains that Thomson's report of five human ES cell lines possessing the characteristics outlined above represents a major technical achievement, since prior to the Thomson et al. publication, it was not a foregone conclusion that ES cells could be derived from human embryos {Gearhart et al. (1998) Science, Vol. 282, 1061-1062, bridging paragraph}. Furthermore, Campbell et al. teaches that, in species other than the mouse the isolation of ES cells has proved more difficult. There are reports of ES-like cell lines in a number of species. However, as yet

there are no reports of any cell lines, which contribute to the germ line in any species other than the mouse {Campbell et al. (1997) Theriogenology, Vol. 47 (1), page 65, paragraph 2}. Thus, based on the art recognized unpredictability of isolating and using embryonic stem cells or other totipotent embryonic cells from mammals, and in view of the lack of guidance provided by the specification for identifying and isolating embryonic cells which can contribute to the germ line of a human the skilled artisan would not have had a reasonable expectation of success in generating any and all totipotent cells, embryonic stem cells, or embryonic germ cells according to the instant invention. Finally, given the art taught unpredictability of using any and all notch ligands to induce T cell lymphopoiesis from progenitor cells, the art taught unpredictability to use any stromal cell to induce development of mature T cells from progenitors, the art taught inability of the *in vitro* system to produce any and all stages of T cell development and any mature T cell, and the lack of working examples and teachings in the art that any embryonic stem cell can be used as a progenitors for T cell lymphopoiesis, the skilled practitioner would be unable to practice the invention as claimed, except as an *in vitro* system comprising stromal cells that express Delta-like 1 ligand, that supports αβ CD4+ CD8+ T cells, αβ CD4- CD8+ T cells and γδ T cell lymphopoiesis but does not support B cell lymphopoiesis, without extensive and arduous experimentation.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-17, 22 and 24 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-17, 22 and 24 of copending Application No. US 10/731, 741. the conflicting claims are identical and therefore are not patentably distinct from each other. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 and 12-15, 17, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Jaleco et al. {Jaleco et al. (2001) J. Exp. Med. 194:991-1001}.

Jaleco et al. provides guidance on an *in vitro* system comprising stromal cells the Delta-1 ligand, which supports T cell lymphopoiesis of hematopoietic progenitor cells (HPCs) but does not support B cell lymphopoiesis (Abstract). Specifically, Jaleco et al. teaches that culturing HPCs with stromal cells that express Delta-1 inhibits B cell differentiation and produces CD3+ CD4+CD8+ T cells (pg. 992, Materials and Methods; pg. 995, Table 1). Abbas et al. teaches that T cells that are CD3+ CD4+CD8+ have inherently undergone TCR V(D)J rearrangement {Abbas et al., (1994) Cellular and Molecular Immunology 2nd ed., 1-457; pg. 176, Fig. 8-5; pg.178 col.

1}. Further, Jaleco et al. teaches that the immature T cells were separated from the aggregate population of cells (pg. 995, Table 1). Thus, by teaching all the limitations of the claims as written, Jaleco et al. anticipates the instant invention as claimed.

Claims 8-11, 16 and 24 are free of the prior art of record.

No claims allowed.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Amy J Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Dr. Louis D. Lieto

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